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Subeschar Antibiotic Infusion in the Treatment of Burn Wound Infection

WILLIAM F. McMANUS, M.D., F.A.C.S., ARTHUR D. MASON, JR., M.D., AND BASIL A. PRUITT, JR., M.D., F.A.C.S.

In a reproducible infected rat burn model, subeschar infusion of antibiotics failed to protect the animals from death via burn wound invasion excepting those animals receiving carbenicillin. Subcutaneous injection of maximal doses of carbenicillin at a distance from the burn wound protected these animals equally well. Some advantage was defined for the subeschar route of administration with suboptimal doses of carbenicillin.

More important is the fact that prospective selection of an effective antibiotic could not be made on the basis of in vitro antibiotic sensitivity tests.

Bacterial invasion of viable subeschar tissue was a major cause of septicemia and death in burned patients before the development of effective topical chemotherapeutic agents (3, 5–7, 9). Such topical agents have significantly reduced but not eliminated the occurrence of burn wound sepsis.

The subeschar infusion of antibiotics has been proposed to prevent and treat burn wound invasion in burn wounds which escape from topical chemotherapeutic control (1). This route of administration offers the theoretical advantage of delivery of concentrations of antibiotic directly into the eschar and tissues immediately beneath a burn wound which may be poorly accessible to systemically administered antibiotics (8). Bacteriologic culture and histologic examination of the burn wound may suggest the appropriate antibiotic to be infused. In this study, we have evaluated the effectiveness of subeschar antibiotic infusion in a reproducible animal burn model (10).

MATERIALS AND METHODS

Two hundred thirty-one Sprague-Dawley rats weighing 180 to 210 gm were anesthetized with intraperitoneal pentobarbital (Table I). Twenty rats were not burned and served as antibiotic controls. Five received carbenicillin, five colistimethate, five gentamicin, and five neomycin subcutaneously daily for 10 days (Table II).

Twenty per cent full-thickness scald burns were inflicted on the remaining 211 rats. Within 1 hour postburn, the wounds were seeded with 1 ml of a trypticase soy broth culture of a lethal strain of *Pseudomonas aeruginosa* (SRU 12-4-4) containing 10^8 organisms per ml. This organism was sensitive, by standard tube dilution techniques, to carbenicillin (312 units/ml), colistimethate (6.2 mcg/ml), gentamicin (3.1 mcg/ml), and neomycin (12.5 mcg/ml). Thirty-one burned seeded rats served as infection controls and received no antibiotics. All antibiotic administration was 24 hours after seeding. Thirty burned seeded rats received carbenicillin, 500 mg/kg subeschar daily for 10 days. Twenty burned seeded rats received colistimethate, 5 mg/kg subeschar daily for 10 days; 20 received gentamicin, 5 mg/kg subeschar daily for 10 days; and 20 received neomycin, 15 mg/kg subeschar daily for 10 days.

In addition, ten burned seeded animals were given carbenicillin, 500 mg/kg subcutaneously, in the anterior abdominal wall at a distance from the burn wound daily for 10 days. Ten burned seeded rats were given a single daily injection of carbenicillin, 500 mg/kg intravenously, and 20 burned seeded animals received carbenicillin, 500 mg/kg as a single daily intraperitoneal injection for 10 days. Ten burned seeded rats were given 250 mg/kg carbenicillin intraperitoneally twice daily for 10 days.

To establish a minimum effective dose of carbenicillin in this model, ten burned seeded rats received carbeni-

TABLE I
Experimental design

231 rats
20 antibiotic controls (A)
Burned seeded
31 infection controls (B)
110 subeschar antibiotics (C)
30 subcutaneous carbenicillin (D)
10 intravenous carbenicillin (E)
30 intraperitoneal carbenicillin (F)

From the United States Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas.

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TABLE II
Results

Group	No. of Animals	Burn %	Seeded	Drug	Dose (mg/kg)	Route	Doses/day	Duration (Days)	Mortality (%)	Mean Day of Death
A	5	No	No	Carb	500	Sc	1	10	0	—
	5	No	No	Col	5	Sc	1	10	0	—
	5	No	No	Gent	5	Sc	1	10	0	—
	5	No	No	Neo	15	Sc	1	10	0	—
B	31	20	Yes	No	—	—	—	—	100	6.3
C	30	20	Yes	Carb	500	Se	1	10	0	—
	20	20	Yes	Col	5	Se	1	10	100	6.5
	20	20	Yes	Gent	5	Se	1	10	100	9.0
	20	20	Yes	Neo	15	Se	1	10	100	7.4
	10	20	Yes	Carb	250	Se	1	10	0	—
	10	20	Yes	Carb	50	Se	1	10	90	8.8
	10	20	Yes	Carb	500	Sc	1	10	0	—
D	10	20	Yes	Carb	250	Sc	1	10	90	10.3
	10	20	Yes	Carb	50	Sc	1	10	100	10.9
E	10	20	Yes	Carb	500	IV	1	10	30	13
F	20	20	Yes	Carb	500	IP	1	10	60	9.8
	10	20	Yes	Carb	250	IP	2	10	30	10.3

Sc = subcutaneous. Carb = Carbenicillin.
Se = subeschar. Gent = Gentamicin.
IV = intravenous. Col = Colistimethate.
IP = intraperitoneal. Neo = Neomycin.

cillin, 250 mg/kg subeschar daily for 10 days; ten received carbenicillin 250 mg/kg subcutaneously (back of neck) daily for 10 days; ten received carbenicillin, 50 mg/kg subeschar daily for 10 days; and ten received carbenicillin, 50 mg/kg subcutaneously daily for 10 days.

RESULTS

All antibiotic controls survived; all infection controls died. All burned seeded animals receiving carbenicillin, 500 mg subeschar, survived. All animals receiving colistimethate, gentamicin, or neomycin subeschar died. The average day of death for those animals receiving colistimethate was 6.5 days, gentamicin 9.0 days, and neomycin 7.4 days (times similar to that of the untreated infected animals). All burned seeded rats receiving carbenicillin 500 mg subcutaneously at a distance from the burn wound survived. Twelve of 20 burned seeded animals receiving single intraperitoneal injections of carbenicillin died, and three of ten burned seeded animals receiving carbenicillin intraperitoneally in divided doses twice daily died. Three of ten animals receiving single daily doses of carbenicillin intravenously died. Nine of ten animals receiving carbenicillin 250 mg subcutaneously died and all animals receiving carbenicillin 50 mg subcutaneously died. All animals treated with carbenicillin 250 mg subeschar survived; nine of ten animals receiving carbenicillin 50 mg subeschar died. These results are shown in Table II.

COMMENT

This animal model has been used for assessment of the effectiveness of prevention of burn wound sepsis after contamination with *Pseudomonas aeruginosa*. We found a moderate advantage in the subeschar route of administration of an effective antibiotic in this reproducible animal burn model. Neomycin, colistimethate, and gentamicin failed to protect the animal when given subeschar even though the organism was sensitive in vitro to each of these drugs. The prospective selection of an effective antibiotic from in vitro sensitivity testing was therefore impossible. Moreover, with maximal dosage no overwhelming advantage for an effective antibiotic (carbenicillin) was found in the subeschar route of administration.

Only carbenicillin, when given subeschar, protected the animals, but it protected animals equally well when given in similar doses subcutaneously, at a distance from the burn wound. Carbenicillin, which like the penicillins, is highly diffusible, is an effective agent for the control of *Pseudomonas* infection (2, 4), and when given in a single injection intravenously or intraperitoneally, or in divided injections intraperitoneally, afforded some protection.

It is likely that the subcutaneous and subeschar routes provide a depot from which a sustained blood level is obtained. The protection afforded by subcutaneous or subeschar administration of carbenicillin appeared to be a function of this sustained absorption and not a specific result of high local antibiotic concentration in the burn wound, even when suboptimal doses were used. The intravenous and intraperitoneal administration of carbenicillin failed to protect the animals.

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